```
19         592 MELOXICAM

=> d hist

     (FILE 'HOME' ENTERED AT 12:04:59 ON 05 NOV 2001)

     FILE 'REGISTRY' ENTERED AT 12:05:32 ON 05 NOV 2001
L1             0 S CELICOXIB
L2             1 S CELEBREX

     FILE 'CAPLUS, MEDLINE' ENTERED AT 12:07:01 ON 05 NOV 2001
L3           504 S L2
L4        135766 S HEPATITIS
L5             7 S L4 AND L3
L6             7 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)
L7          5527 S COX-2
L8          5823 S CYCLOOXYGENASE-2 OR CYCLOOXYGENASE (W) (2 OR II)
L9          7537 S L8 OR L7
L10           24 S L9 AND L4
L11           20 DUPLICATE REMOVE L10 (4 DUPLICATES REMOVED)
L12       340843 S ANTI-INFLAMM? OR INFLAMMAT?
L13         3966 S L12 AND L9
L14          911 S L13 AND INFLAMMAT?/TI
L15          110 S L14 AND COX-2/TI
L16            0 S L15 AND LIVER
L17           29 S L15 AND PY<=1997
L18           21 DUPLICATE REMOVE L17 (8 DUPLICATES REMOVED)
L19          592 S MELOXICAM

=> s l19 and l4
L20            2 L19 AND L4
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=> s anti-inflamm? or inflammat?
L12     340843 ANTI-INFLAMM? OR INFLAMMAT?

=> d hist

     (FILE 'HOME' ENTERED AT 12:04:59 ON 05 NOV 2001)

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L2            1 S CELEBREX

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L3          504 S L2
L4       135766 S HEPATITIS
L5            7 S L4 AND L3
L6            7 DUPLICATE REMOVE L5 (0 DUPLICATES REMOVED)
L7         5527 S COX-2
L8         5823 S CYCLOOXYGENASE-2 OR CYCLOOXYGENASE (W) (2 OR II)
L9         7537 S L8 OR L7
L10          24 S L9 AND L4
L11          20 DUPLICATE REMOVE L10 (4 DUPLICATES REMOVED)
L12     340843 S ANTI-INFLAMM? OR INFLAMMAT?

=> s l12 and l9
L13        3966 L12 AND L9

=> s l13 and inflammat?/ti
L14         911 L13 AND INFLAMMAT?/TI

=>

=> s l14 and cox-2/ti
L15         110 L14 AND COX-2/TI

=> s l15 and liver
L16           0 L15 AND LIVER

=> s l15 and py<=1997
L17          29 L15 AND PY<=1997
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WEST

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Today's Date: 11/5/2001

DB Name	Query	Hit Count	Set Name
JPAB,EPAB,DWPI	l22 and l21	17	L23
JPAB,EPAB,DWPI	hepatitis	9504	L22
JPAB,EPAB,DWPI	l17 or l18 or l19 or l20	506	L21
JPAB,EPAB,DWPI	cyclooxygenase adj II	26	L20
JPAB,EPAB,DWPI	cyclooxygenase adj 2	372	L19
JPAB,EPAB,DWPI	cyclooxygenase-2	345	L18
JPAB,EPAB,DWPI	cox-2	298	L17
USPT	l7 and l13	36	L16
USPT	l7 and l2	21	L15
USPT	l13 and l2	0	L14
USPT	hepatitis	12548	L13
USPT	l8 and l2	3	L12
USPT	l8.clm. and l7.clm.	2	L11
USPT	l8 and l7.clm.	13	L10
USPT	l8 and l7	88	L9
USPT	liver or hepatitis or cirrhosis or steatohepatitis	43017	L8
USPT	l3 or l4 or l5	301	L7
USPT	s l3 or l4 or l5	301	L6
USPT	cyclooxygenase adj II	51	L5
USPT	cyclooxygenase adj 2	254	L4
USPT	cyclooxygenase-2	229	L3
USPT	5466823	30	L2
USPT	5466823.pn.	1	L1

L18 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
ACCESSION NUMBER: 1996:356036 CAPLUS
DOCUMENT NUMBER: 125:31441
TITLE: Selective inhibition of cyclooxygenase (**COX**)-**2** reverses **inflammation** and expression of **COX-2** and cyclooxygenase (**COX**)-**2** in rat adjuvant arthritis
AUTHOR(S): Anderson, Gary D.; Hauser, Scott D.; McGarity, Kelly L.; Bremer, Margaret E.; Isakson, Peter C.; Gregory, Susan A.
CORPORATE SOURCE: Dep. of Inflammatory Diseases Res. and Cell and Molecular Biology, G.D. Searle & Company, St. Louis, MO, 63198, USA
SOURCE: J. Clin. Invest. (**1996**), 97(11), 2672-2679
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prostaglandins formed by the cyclooxygenase (COX) enzymes are important mediators of **inflammation** in arthritis. The contribution of the inducible **COX-2** enzyme to **inflammation** in rat adjuvant arthritis was evaluated by characterization of **COX-2** expression in normal and arthritic paws and by pharmacol. inhibition of **COX-2** activity. The injection of adjuvant induced a marked edema of the hind footpads with coincident local prodn. of PGE2. PG prodn. was assocd. with upregulation of **COX-2** mRNA and protein in the affected paws. In contrast, the level of COX-1 mRNA was unaffected by adjuvant injection. TNF-.alpha. and IL-6 mRNAs were also increased in the inflamed paws as was IL-6 protein in the serum. Therapeutic administration of a selective **COX-2** inhibitor, SC-58125, rapidly reversed paw edema and reduced the level of PGE2 in paw tissue to baseline. Interestingly, treatment with the **COX-2** inhibitor also reduced the expression of **COX-2** mRNA and protein in the paw. Serum IL-6 paw IL-6 mRNA levels were also reduced to near normal levels by SC-58125. Furthermore, inhibition of **COX-2** resulted in a redn. of the **inflammatory** cell infiltrate and decreased **inflammation** of the synovium. Notably, the antiinflammatory effects of SC-58125 were indistinguishable from the effects obsd. for indomethacin. These results suggest that **COX-2** plays a prominent role in the **inflammation** assocd. with adjuvant arthritis and that **COX-2** derived PGs upregulate **COX-2** and IL-6 expression at **inflammatory** sites.

L8 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:512202 CAPLUS
DOCUMENT NUMBER: 125:184577
TITLE: **COX-2** inhibitors. Potential for reducing NSAID side-effects in treating **inflammatory** diseases
AUTHOR(S): Carty, T. J.; Marfat, A.
CORPORATE SOURCE: Central Research Division, Pfizer, Inc., Groton, CT, 06340, USA
SOURCE: Emerging Drugs (**1996**), 1, 391-411
CODEN: EMDRFV; ISSN: 1361-9195
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 82 refs. Downregulation of prostaglandin (PG) formation is essential for the removal of the painful symptoms of **inflammation**, ranging from sports injuries to rheumatoid arthritis. Nonsteroidal **anti-inflammatory** drugs (NSAIDs, e.g., indomethacin, piroxicam), are well recognized to be clin. efficacious by controlling PG formation through the inhibition of cyclooxygenase (COX), a key enzyme in the PG synthetic cascade. The use of NSAIDs, however, can be limited by their gastrointestinal (GI) and renal side-effects, esp. in the elderly. Recent research has shown that cellular synthesis of PG is derived from two different forms of COX, a constitutive (naturally present) isoform (COX-1) used for the maintenance of organ function (e.g., the GI tract), and an inducible isoform (**COX-2**) employed for the prodn. of large amts. of PG synthesized during **inflammation**. Since most NSAIDs inhibit both isoforms, this finding has provided a unique opportunity to discover a pharmacol. agent with specificity for inhibiting **COX-2**, with little or no effect on COX-1. While retaining the efficacy of conventional NSAIDs, **COX-2**-selective NSAIDs are expected to display no deleterious effects on the GI tract, thus providing significantly improved toleration. Although it is not clear what their effect will be on the kidney, **COX-2**-selective agents should offer a pharmacol. profile that predominantly targets PGs produced at the **inflammatory** site. Should ongoing clin. trials prove the **COX-2** concept, this class of compds. could provide a new and exciting generation of **anti-inflammatory** drugs, which, we would like to propose, could be called **COX-2**-SAIDs, for **COX-2**-selective **anti-inflammatory** drugs.

L11 ANSWER 13 OF 38 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:33593 CAPLUS
DOCUMENT NUMBER: 128:162452
TITLE: Clinical pharmacokinetics of nabumetone: the dawn of selective cyclo-oxygenase-2 inhibition?
AUTHOR(S): Davies, Neal M.
CORPORATE SOURCE: Faculty of Medicine, Department of Pharmacology and Therapeutics, Intestinal Disease Research Unit, University of Calgary, Calgary, AB, Can.
SOURCE: Clin. Pharmacokinet. (**1997**), 33(6), 403-416
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 45 refs. Nabumetone is a nonsteroidal anti-inflammatory drug (NSAID) of the 2,6-disubstituted naphthyl-alkanone class. Nabumetone is metabolized to an active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) which is a relatively selective cyclo-oxygenase-2 inhibitor that has anti-inflammatory and analgesic properties. Nabumetone and its metabolites bind extensively to plasma albumin. Nabumetone is eliminated following biotransformation to 6-MNA, which does not undergo **enterohepatic** circulation and the resp. glucoroconjugated metabolites are excreted in urine. Substantial concns. of 6-MNA are attained in synovial fluid, which is the proposed site of action in chronic inflammatory arthropathies. A smaller area under the plasma concn.-time curve (AUC) is evident at steady state as compared with a single dose; this is possibly due to an increase in the vol. of distribution and satn. of protein binding. Relationships between 6-MNA concns. and the therapeutic and toxicol. effects have yet to be elucidated for this NSAID. Renal failure significantly reduces 6-MNA elimination but steady-state concns. of 6-MNA are not increased, possibly because of nonlinear protein binding. Elderly patients with osteoarthritis demonstrate decreased elimination and increased plasma concns. of nabumetone as compared with young healthy volunteers. Rheumatic disease activity also influences 6-MNA plasma concns., as patients with more active disease and lower serum albumin concns. demonstrate a lower area under the plasma concn. vs. time curve. A reduced bioavailability of 6-MNA in patients with severe **hepatic** impairment is also evident. Dosage adjustment may be required in the elderly, patients with active rheumatic disease and those with **hepatic** impairment, but not in patients with mild-to-moderate renal failure.

L11 ANSWER 20 OF 38 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 97362852 MEDLINE
DOCUMENT NUMBER: 97362852 PubMed ID: 9219316
TITLE: Meloxicam: selective **COX-2** inhibition in clinical practice.
AUTHOR: Furst D E
CORPORATE SOURCE: Arthritis Clinical Research Unit, Virginia Mason Research Center, Seattle, WA 98101, USA.
SOURCE: SEMINARS IN ARTHRITIS AND RHEUMATISM, **(1997 Jun)** 26 (6 Suppl 1) 21-7. Ref: 24
Journal code: UMV; 1306053. ISSN: 0049-0172.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970902
Last Updated on STN: 19970902
Entered Medline: 19970819

AB Nonsteroidal antiinflammatory drugs (NSAIDs) exert their actions by inhibiting cyclooxygenase (COX). It has recently been postulated that NSAIDs' antiinflammatory efficacy arises from inhibition of the **COX-2** isoform of cyclooxygenase, whereas inhibition of the COX-1 isoform produces the troublesome and sometimes serious gastric and renal side effects of NSAIDs. A relatively selective **COX-2** inhibitor, such as meloxicam, may combine antiinflammatory efficacy with improved tolerability. In volunteers, indomethacin 75 mg, but not meloxicam 7.5 mg, inhibited renal prostaglandin E2 excretion and platelet aggregation (COX-1 mediated effects). Double-blind, randomized trials in osteoarthritis and rheumatoid arthritis patients have shown equivalent antiinflammatory efficacy among meloxicam 7.5 mg or 15 mg and diclofenac 100 mg, naproxen 750 mg, and piroxicam 20 mg. In a double-blind, placebo-controlled trial, meloxicam (7.5 or 15 mg) caused less endoscopically detected gastrointestinal (GI) damage (Lanza scale) than piroxicam 20 mg. The MELISSA study, a double-blind, randomized, 28-day trial in over 9,000 patients showed that meloxicam 7.5 mg caused statistically less total GI toxicity, dyspepsia, abdominal pain, nausea and vomiting, and diarrhea than diclofenac 100 mg, despite equivalent reductions in pain on movement for each treatment. A global safety analysis of clinical trials, representing over 5,600 patients and comprising 170 and 1,100 patient-years of exposure for meloxicam 7.5 mg and 15 mg, respectively, showed that meloxicam caused less GI toxicity and fewer peptic ulcers and GI bleeds than naproxen, diclofenac, or piroxicam.

The renal safety profile and incidence of **liver** function abnormalities with meloxicam is equivalent to other NSAIDs available for clinical use. In conclusion, relatively selective **COX-2** inhibition exemplified by meloxicam may offer effective symptom relief with an improved GI tolerability profile.

ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:562995 CAPLUS
DOCUMENT NUMBER: 127:225303
TITLE: Immunosuppressive combinations containing a **cyclooxygenase-2** inhibitor and a leukotriene A4 hydrolase inhibitor
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729774	A1	19970821	WO 1997-US1421	19970211 <--
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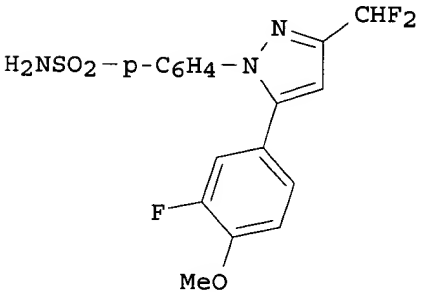
EP 880363	A1	19981202	EP 1997-907545	19970211
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001506574	T2	20010522	JP 1997-529358	19970211

PRIORITY APPLN. INFO.: US 1996-600655 A1 19960213
WO 1997-US1421 W 19970211
OTHER SOURCE(S): MARPAT 127:225303
GI



I

AB Immunosuppressant compns. contg. a combination of a **cyclooxygenase -2** inhibitor (which inhibits conversion of arachidonic acid to prostaglandins) and a LTA4 hydrolase inhibitor are useful in reducing recipient rejection of **transplanted** organs and for treatment of autoimmune diseases. Thus, F2CHCO2Et reacted with 3-fluoro-4-

methoxyacetophenone to form 4,4-difluoro-1-(3-fluoro-4-methoxyphenyl)butane-1,3-dione, which was condensed with 4-sulfonamidophenylhydrazine-HCl to produce the **cyclooxygenase-2** inhibitor I. A formulation was prepd. contg. 350 mg I and 700 mg 3-[N-methyl-N-[3-[(4-phenylmethyl)phenoxy]propyl]amino]propanoic acid (LTA4 hydrolase inhibitor).

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:562996 CAPLUS
DOCUMENT NUMBER: 127:239123
TITLE: Combinations having immunosuppressive effects, containing **cyclooxygenase-2** -inhibitors and 5-lipoxygenase inhibitors
INVENTOR(S): Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
PATENT ASSIGNEE(S): G.D. Searle & Co., USA; Gregory, Susan A.; Isakson, Peter C.; Anderson, Gary
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9729776	A1	19970821	WO 1997-US1558	19970212 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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JP 2000504723	T2	20000418	JP 1997-529363	19970212

PRIORITY APPLN. INFO.: US 1996-600622 A1 19960213
WO 1997-US1558 W 19970212
OTHER SOURCE(S): MARPAT 127:239123

AB Treatment with a **cyclooxygenase-2** inhibitor and a 5-lipoxygenase inhibitor is described as being useful in reducing recipient rejection of **transplanted** organs and for treatment of autoimmune diseases. 4-[5-(3-Fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide and N'-[3-[5-(4-fluorophenoxy)-2-furyl]-1-methyl-2-propynyl]-N'-hydroxyurea were prepd. and a combination of these 2 compds. showed a delay in rejection time of skin grafts while treatment alone of each of these compds. resulted in no prolongation of graft survival.